MARKED-UP COPY OF AMENDED CLAIMS:

Please amend the claims as follows:

10. (AmendedNew) A drug composition for continuous, or progressive, or continuous and progressive administration to a subject orally, subcutaneously, transdermally, or any combination thereof, comprising as a first component, nicotine or a nicotine derivative; and ~~at least one~~ a second component comprising ~~selected from the group consisting of~~ L-DOPA ~~and dopaminergic agonists~~.

11. (AmendedNew) The drug composition of claim 10 wherein said second component ~~is~~ includes L-DOPA.

12. (AmendedNew) The drug composition of claim 10 wherein said second component further comprises a dopaminergic agonist ~~is selected from the group consisting of bromocriptine and biperiden~~.

13. (AmendedNew) The drug composition of claim 12 wherein said ~~second component is L-DOPA and at least one~~dopaminergic agonist is selected from the group consisting of bromocriptine, pyribedil and ~~or~~ biperiden.

15. (AmendedNew) A method for improving the functionality of D1 and D2 dopaminergic receptors associated with neurodegenerative diseases, multi-systemic atrophies or both, comprising administering to a subject over a long term period an effective dose of at least two drug components comprising as a first component nicotine or a nicotine derivative, and ~~at least one~~ a second component comprising at least one member selected from the group consisting of L-DOPA and dopaminergic agonists.

18. (AmendedNew) The method of claim 16~~17~~ wherein said D1 and D2 dopaminergic receptors are associated with neurodegenerative diseases.

21. (Amended~~New~~) The method of claim 20 wherein said second component of said drug composition is L-DOPA and at least one compound selected from the group consisting of bromocriptine, pyribedil and ~~or~~ biperiden.

22. (Amended~~New~~) The method of claim 16~~17~~ wherein said drug composition is administered transdermally, subcutaneously, extracoporeally or orally.

24. (Amended~~New~~) The method of claim 20 wherein said ~~at least~~ first component is administered at a gradually increasing rate.

28. (Amended~~New~~) A method for treating a neurodegenerative disease, a multi-systemic atrophy, or both, in a human mammal comprising administering over a long term period an effective dose of at least two drug components comprising as a first component, nicotine or a nicotine derivative, and ~~at least one~~ a second component comprising at least one member selected from the group consisting of L-DOPA and dopaminergic agonists.

30. (Amended~~New~~) The method of claim 28~~29~~ wherein said second component of said drug composition is L-DOPA.

31. (Amended~~New~~) The method of claim 30 wherein said second component of said drug composition is L-DOPA and at least one compound selected from the group consisting of bromocriptine, pyribedil and ~~or~~ biperiden.

33. (Amended~~New~~) The method of claim 28~~29~~ wherein said drug composition is administered transdermally, subcutaneously, extracoporeally or orally.

35. (AmendedNew) The method of claim 30 wherein said ~~at least~~ first component is administered at a gradually increasing rate.

REMARKS

Entry of the formal drawings and claim amendments is respectfully requested; no new matter is added. Support for the inclusion of pyribedil as a dopaminergic agonist can be found on page 1, last full paragraph. Cancelled claims and adjusted dependencies are responsive to the Examiner's comments and will be further discussed hereinbelow. Claims 24 and 35 have been amended to delete an incorrect reference to "at least" with regard to the first component. New claims 39-49 have been added to appropriately claim the invention in view of the amendments responsive to the Office Action and the cited art. Support for the lower limit of nicotine concentration in claim 40 can be found in the stabilized dose of Example 1 and the fact that the patient weighed 65 kg. The other concentration ranges appearing in the claims are expressed in the specification. Support for new dependent claim 49 can be found on page 4, last sentence.

Claims 10-38 have been rejected under 35 U.S.C. § 112, second paragraph. The bases for this rejection appear in a series of remarks beginning on page 2 of the Office Action. Each remark will be addressed in the order to which it appears. The questions or comments and each response thereto is set forth serially. Reconsideration and withdrawal of the rejections is requested in view of the amendments and remarks herein:

1. Comment: How, in claims 10-38 can there be "two second components?"

Response: It is respectfully noted that the language of the claims and particularly that in claims 10, 15 and 28 has been clarified in view of the Examiner's comment.

2. Comment: "Janson et al. discloses that nicotine is a dopaminergic agonist."

Response: It is respectfully noted that the cited Janson et al. reference does not disclose that nicotine is

a dopaminergic agonist. On the contrary, Janson et al. disclose that nicotine is known as an agonist of cholinergic receptors (page 25, second column, last sentence). Furthermore, nicotine and its derivatives are similarly described in the present application (page 2, last sentence) and also as "nicotinergic agonists" (page 3, second full paragraph).

3. Comment: It is not clear in claim 12 that the dopaminergic agonist is required.

Response: Claim 12 has been amended to specifically require the presence of a dopaminergic agonist.

4. Comment: There is no antecedent basis in claim 12 for the "second component" of claim 13.

Response: Claim 13 has been further amended; this rejection is moot.

5. Comment: No subject or effective amount is recited in claim 15.

Response: Claim 15 includes a reference to administering "an effective dose." As would be readily understood by one skilled in the art, such a dose will depend not only on the patient's body weight, but also on other factors relating to prior medical history, other drugs being taken, the severity of the condition, the type and efficacy of the administered compounds, etc. These are all factors ordinarily considered by a skilled medical practitioner and readily determined using both the teachings of the specification, the experience of the practitioner and limited "experimentation," i.e., prescribing a dose and adjusting it, if necessary, based on the response observed in the patient. Additionally, claim 15 has been amended to include reference to a "subject." Withdrawal of this objection is respectfully requested.

6. Comment: Claims 17, 29 and 38 do not further limit the claims from which the depend since the term "long-term" is defined in the specification.

Response: Claims 17 and 29 have been deleted. As observed by the Examiner, "long-term" is defined in the specification. Furthermore, claim 38 further limits the claim from which it depends since it recites a term of "at least about four months." (Emphasis added.)

7. Comment: Regarding claims 15, 17 and 18, it is noted that the word "improving" is relative. Furthermore, it is questioned whether the subject must have more than one disease and it is stated that it is inherent that D1 and D2 dopaminergic receptors are associated with neurodegenerative disease.

Response: While the D1 and D2 receptors are associated with neurodegenerative diseases, they are not associated solely with such diseases. For example, such receptors are associated with other conditions and cognitive processes such as drug addiction, memory and learning. Consequently, further amending claim 15 as suggested would be unnecessarily limiting. Furthermore, while use of the term "improving" is relative, in the present application performance can be measured as described so that one skilled in the art would understand the scope and meaning of the term.

8. Comment: No effective amount is recited in claim 28.

Response: Please refer to the comments in paragraph 5 above concerning the same issue with regard to claim 15.

9. Comment: In claim 32, the recitation "and/or" is confusing. The Examiner relies on *In re Anderegg*, 51 U.S.P.Q. 66.

Response: It is respectfully suggested that the term "and/or" as used in the present context in claim 32 is

clear. The Examiner has not suggested how the term could be confused when interpreting the claim and it is not apparent how such confusion may arise. The term is being used in the claim in its ordinary sense as defined in standard dictionaries, e.g., (1) Webster's Unabridged or (2) Random House:

(1) and/or - Either *and* or *or*. "Butter and/or eggs" means "butter and eggs, or butter or eggs."

(2) and/or - Used to indicate that either "and or "or" is appropriate for linking two words, phrases or the like" *insurance to cover fire and/or theft*.

Copies of these references are enclosed for the Examiner's convenience. Furthermore, while *In re Anderegg* has not been overturned since the date of the decision, October 1940, it has never been followed and the use of alternative expressions in claiming is now looked upon more favorably, as suggested in the MPEP (2.73.05(h)) and by the courts (*Chisum on Patents*, Section 8.06[2][a] "Alternative Limitations").

In summary, and in view of the claim amendments and above remarks, withdrawal of the rejections under 35 U.S.C. § 112 is respectfully requested.

Turning now to the rejection in view of prior art, "claims 10-38 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Janson et al. or applicants' admissions." This rejection is traversed and reconsideration is requested.

Although this response accurately quotes the rejection as presented in the Office Action, it appears from the context of the rejection as further explained by the Examiner (pages 3 and 4 of the Office Action), that it was the Examiner's intention not to rely on Janson et al., but to rely instead on the Domino et al. reference (hereinafter "Domino"). In the

comments that follow, applicants have treated the rejection under § 103(a) in view of Domino.

The Examiner asserts that "Domino (abstract, among others) and applicants (pages 2-3) disclose that both nicotine and its derivatives and L-DOPA and dopaminergic agonists, alone and in combination, are useful to treat neurodegenerative disease." Applicants take exception to the oversimplification of Domino and to the inaccurate representation of their own teaching. With regard to the latter, applicants explicitly state:

> "Further, the development of a treatment associating nicotine or its derivatives, L-DOPA and D2 receptor agonists has never been researched." (Page 3, lines 7-9; emphasis added.)

Additionally, while applicants did not refer to Domino in the specification, their comments relating to another study are similarly applicable to Domino:

> "However, none of the nicotine treatment trials which have been conducted concerned long-term treatment without interruption." (Page 3, lines 4-6.)

This observation applies to Domino even though Domino included L-DOPA or a D2 agonist. Furthermore, the Examiner acknowledges that the instant claims differ from Domino "in reciting specific combinations, forms and amounts of compositions, duration of treatment and routes of administration." (Page 3.)

While the extent of these differences should be sufficient to distinguish over Domino, the Examiner further suggests that there is an "absence of a showing of unobvious results" and that such deficiencies could be cured by a Declaration. Additionally, the Examiner states that the Examples "are not persuasive" and that "duration of treatment

and routes of administration are within the skill of the artisan." These views are traversed.

To begin with, it is necessary to more thoroughly characterize the teaching of Domino and by doing so, applicants' advance will be clearly seen. The following are noted:

a. Domino worked with monkeys rather than human subjects and relied on changes in circling behavior to evaluate an improvement. Such criteria differ significantly from the UPDRS methods described in the specification (page 5, last paragraph to page 6, third paragraph). Consequently, the model used in Domino is not necessarily a predictor or indicator of success as suggested in Domino's own conclusions (Abstract, last sentence) versus the present findings. Even Domino questioned the animal model and test method (page 419, first full sentence). Such a questionable teaching can hardly be sufficient under 35 U.S.C. § 103(a) to render the present claims obvious.

b. The Domino data are obtained from Parkinson's disease induced by MPTP. The impact of such an agent on the subject, the symptoms and on the drugs used to treat the condition are not defined. Furthermore, the subjects used by Domino had been previously exposed to a wide array of other damaging chemical agents and their impact is indeterminate (page 415, column 1, first paragraph). In contrast, the subjects of the present invention suffered from and were treated for idiopathic, non-induced Parkinson's disease, among other conditions. Consequently,

the relevance of Domino to the present invention is questionable.

c. Of particular importance, the duration of treatment is significantly different in the claims of the present invention compared to Domino. In Domino, it appears that treatment continued for three weeks (page 415, "Results") although there is no explicit statement of treatment duration and Domino did not consider the effect of further extended treatment at all.

In contrast, it is the long-term treatment of the present invention that distinguishes it over the prior art including Domino. Note the present teaching, "It is essential that treatment with the drugs of the invention is a long-term treatment" (page 6, fourth paragraph). There is nothing in Domino to suggest such long-term treatment and certainly nothing in the reported results that would motivate one skilled in the art to extend the treatment as herein claimed.

d. The drug combinations in Domino differ from those presently claimed and the reference does not suggest others.

Considering a more comprehensive understanding of Domino, the present claims are clearly distinguished over the reference.

While the Examiner finds the experimental evidence in the present invention to be inadequate, it appears that applicants' observations including the figures, tables and conclusions have not been duly considered. For example:

> "In conclusion, comparing the results obtained with the drug of the invention, administered together with L-DOPA in sub-active doses, it appears that, <u>for the first</u>

> time, patients experience a re-establishment, reduction or complete stop to syndromes characterizing Parkinson's disease and associated diseases. The results of the UPDRS I, II and III tests also show clear re-establishment of dopaminergic and nicotinergic functions which allows long-term stabilization of these improvements to be presumed. (Page 11, last paragraph to page 12; emphasis added.)

Applicants have achieved an advance in the treatment of diseases by building on the limited teachings of the prior art and utilizing a treatment regimen that did not exist. The teachings of Domino are inadequate to render the present claims obvious under accepted standards applied to 35 U.S.C. § 103(a). Even selecting limited portions from the reference and extrapolating to applicants' claims does not cure the conclusions of the reference that the drug combination used there and the treatment period did not achieve the desired results. The present claims are allowable over Domino.

Furthermore, new claims 39-49 are directed to various aspects of the claimed drug composition and are distinguished from, and patentable over, the limited disclosure of Domino. In particular, Domino provides for a combination of L-DOPA and nicotine as intramuscular ("im") injections and does so using high concentrations of L-DOPA (p. 45, col. 2, last paragraph). Furthermore, the im dosage form of Domino is not administered as long-term, continuous treatment and so the drug composition is merely a single concentration administered rapidly (essentially "instantly") to the subject. The modest improvement observed in Domino was "perplexing" to the authors (p. 417, col. 2, second full paragraph) and does not suggest or encourage one skilled in the art to take the distinguishing steps employed herein to achieve the significant improvement in patient behavior as reported.

Withdrawal of the rejection under 35 U.S.C. § 103(a) of the amended claims in view of the remarks is respectfully requested.

As it is believed that all of the rejections set forth in the Official Action have been fully met, favorable reconsideration and allowance are earnestly solicited.

If, however, for any reason the Examiner does not believe that such action can be taken at this time, it is respectfully requested that he telephone applicant's attorney at (908) 654-5000 in order to overcome any additional objections which he might have.

If there are any additional charges in connection with this requested amendment, the Examiner is authorized to charge Deposit Account No. 12-1095 therefor.

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Respectfully submitted,

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